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# THE FERMENT ACTIVITY OF THE BLOOD SERUM IN INFECTIOUS DISEASES *

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It has been shown that blood serum under various conditions has the power of splitting proteins into less complex compounds. E. Abderhalden[1] has proved this to be true of the serum of pregnant women, and of that of patients suffering from carcinoma. He is supported and his work has been confirmed by a great many observers, both in Europe and in this country. Fauser,[2] Flatow,[3] and many others have demonstrated ferment activity in the blood in cases of dementia praecox, epilepsy, and other nervous affections.

In this country Williams and Pearce, Jellinghaus and Losee, Schwartz, McCord, and others, report similar results. Jobling, Eggstein, and Petersen[4] have shown that normal guinea-pig serum contains active tryptic ferments which can be demonstrated, after removing the antitryptic substances, by treating the serum with various agents, such as kaolin, starch, and iodin, and then allowing the serum to act on preparations of casein.

In a recent article I[5] have shown that by the dialysis method ferments can be detected in the serum in a large number of pathological conditions, as well as during pregnancy, and at the height of digestion; also that apparently normal individuals occasionally give positive reactions. I pointed out that the length of time in the dialyzer has much to do with the occurrence of a positive or negative reaction. S. Kjaergaard[6] has supported this in a recent article; he also confirms my findings of positive reactions in other conditions, as carcinoma, but he has not reported experiments with sera from infectious diseases. Fränkel[7] supports my view entirely; he found that sera from various pathological conditions usually gave positive reactions.

* Received for publication April 5, 1915.

1. Abwehrfermente.
2. München. med. Wchnschr., 1914, 61, p. 126.
3. Ibid., p. 1168.
4. Jour. Exper. Med., 1915, 21, p. 239.
5. Jour. Am. Med. Assn., 1914, 63, p. 1172.
6. Ztschr. f. Immunitätsforsch. u. exper. Therap., 1914, 22, p. 31.
7. Ibid., p. 549.

The work now reported was undertaken with the idea of determining what pathological conditions cause an increase in the ferment content of the blood that could be detected by the dialysis method, placenta being used as a substrate. It was decided systematically to investigate a number of conditions, examining enough cases of each to warrant drawing conclusions, in the hope that by this means some light might be shed on the underlying principles of infection and immunity in the various pathological conditions examined.

In investigating a disease, two objects were especially observed: (1) the presence or absence of the ferments as indicated by positive or negative reaction; (2) relative strength of the reaction compared with the stage, and clinical severity of the disease.

Lobar pneumonia was the first disease investigated. There is reason to believe that the crisis in this disease is due to the rapid mobilization of a large amount of powerful ferment in the blood stream. Indeed Dick[8] has shown that proteolytic ferments develop in the blood during pneumonia, about the time of crisis. He notes also that the ferments seem to have a special action upon pneumococcus protein. In this work, the tryptic power of the serum was determined by the polariscope. I assumed that if these ferments were not absolutely specific, their presence ought to be capable of demonstration by the dialysis method, properly prepared placental tissue being used as a substrate.

The technic followed was that given by Abderhalden;[9] and inactivated serum plus placenta was used as a control in each case. The controls were uniformly negative. For excellent English descriptions of the technic, reference may be made to articles by H. Schwartz,[10] and Jellinghaus and Losee.[11]

A few points in technic that gave most trouble in the early part of this work and which have been called to my attention as sources of error by other workers in this field, may be mentioned here:

(*a*) Apparatus and glassware must be scrupulously clean, physically and chemically.

(*b*) Blood serum must be fresh, and absolutely free from hemolysis.

(*c*) Bacterial contamination of the serum must be avoided as much as possible; and the growth of bacteria prevented by generous use of toluene.

(*d*) Incubation should be allowed to proceed twenty to twenty-four hours instead of sixteen to eighteen hours, as was originally advised by Abderhalden.[12] He now also uses the longer period in his work.

(*e*) Instead of 1.5 or 2 c.c. of serum, as Abderhalden advocated at first, 1 c.c. of serum is used. He now advises the lesser amount.

8. Jour. Infect. Dis., 1912, 10, p. 383.
9. Beitr. z. Klin. d. Infectionskrank. u. Immunitätsforsch., 1913, 1, p. 243.
10. Am. Jour. Obst., 1914, 69, p. 54.
11. Ibid., p. 593.
12. München. med. Wchnschr., 1914, 61, p. 8.

(*f*) After each time that the dialyzing thimbles are used, they should be washed scrupulously clean, and allowed to stand several hours in fresh distilled water, so that any digestion products may dialyze out of the tube wall, and all the serum be cleansed away.

(*g*) The dialyzing thimbles are best kept under water in a large jar and brought to boil just before using. Prolonged boiling is said to alter the permeability of the membranes, rendering them thicker.

(*h*) The placenta must be obtained fresh.

I start the preparation within a few seconds after the birth of the placenta. The amnion and cord are dissected off rapidly, and the remaining tissue is cut into pieces the size of a hazelnut. These are placed in a piece of gauze about one foot square and two or three layers thick. The edges are folded up to make a bag, and the tissue is washed in cold running water, or in frequently changed water, until the wash water remains absolutely clear. During this process the tissue is constantly kneaded and pressed between the hands. The bag is then opened and any pieces of tissue containing clotted blood are discarded; pieces having a pink tinge are broken up into smaller pieces, and the washing repeated until the tissue appears absolutely free from blood. Now pieces of tissue with the faintest tinge of pink are discarded, and the rest placed in about a liter of boiling water. The washing takes about two to two and one-half hours, and must be uninterrupted. After boiling for five minutes, the water is poured off, and the tissue is washed in several changes of water, being well squeezed by the hands in each to remove all the extracts from the tissues. The tissue is again boiled for five minutes and the washing repeated. This is repeated about six times; then the tissue is boiled with five times its volume of water for five minutes. Next 5 c.c. of the filtrate is tested with 1 c.c. of a 1 percent ninhydrin solution by boiling for one minute. If any violet color is noted in this fluid after standing one-half hour, the boiling and washing should be repeated three or four times. In the event, as sometimes happens, that the filtrate as obtained above still gives the reaction, it is best to discard this tissue, and prepare another placenta. It has been found by others as well as myself that some placentae apparently cannot be freed from substances reacting with ninhydrin, by the method herein described. When the filtrate from the boiled placenta no longer gives the faintest trace of color on boiling with ninhydrin as described, the tissue is boiled once more in fresh distilled water, placed in sterile, colored bottles, and covered with boiling water. It is then cooled to room temperature, and two drams of chloroform added to each eight-ounce bottle. If the chloroform is added before cooling the jars, it will boil away rapidly. Toluene is now added to form a layer about one-eighth of an inch thick on the surface of the fluid. Enough tissue for immediate needs is removed with sterile forceps from the stock bottles before setting up each experiment, and is boiled three times in three changes of water before using in a test. It is well to test 5 c.c. of the filtrate from the last boiling with 1 c.c. of a 1 percent solution of ninhydrin to be sure that the tissue just before going into the test is absolutely free from dialyzable, ninhydrin-reacting substances.

This work when properly done is tedious and time consuming; nor can it be done in bulk. Each test requires individual attention at all stages to insure uniformity, and to avoid errors in the technic. Various modifications in the technic at the present stage of our knowledge are inadvisable, because they render the work of the various investigators impractical for comparison. The technic is not too difficult for any well-trained person to master, but personal attention to each detail of preparation for and carrying out of the test is

necessary, and no part of the work can be entrusted to unskilled assistants, or persons not familiar with the theoretical principles underlying the test. For example, results obtained by men using serum collected by someone else at a distance from the laboratory, and often forty-eight or more hours old when used, are of no possible significance.

## DISEASES

*Pneumonia.*—Nineteen cases of lobar pneumonia were studied. Five cases before the crisis, third to seventh day, were observed. The reaction was negative in one, and weakly positive in another, in which the blood was taken on the third and fourth days respectively, and the dialysis allowed to proceed twenty and twenty-one hours. The reaction was moderately strong in two of the remaining cases, and strong in the third; but in these instances dialysis proceeded twenty-seven hours.

Blood was obtained during lysis in two cases, one of which gave a very strong reaction, the other a moderately strong one.

Blood was obtained also from twelve cases at varying periods after defervescence, from one day to four and one-half weeks. In this group the reactions were very strong in most cases shortly after the crisis, and progressively weaker as convalescence was established. It was negative in one case one week after crisis. The varying strength of reaction and period of dialyzation will be seen in Table 1. Case 6 is especially interesting, because clinically it was an unresolved pneumonia, and, as might be expected theoretically, gave a weak reaction.

TABLE 1

LOBAR PNEUMONIA

| Number | Day of Disease | Time Since Last Meal in Hours | Time of Incubation in Hours | Ninhydrin Reaction | Control Reaction | Sex | Age | Remarks |
|---|---|---|---|---|---|---|---|---|
| | | | | | I.S+P | | | |
| 1 | 3 | 6 | 20 | 0 | 0 | | | |
| 2 | 4 | 4 | 21 | + very weakly positive | 0 | M | 25 | |
| 3 | 4 | 4 | 27 | ++++ | 0 | M | 43 | |
| 4 | 5 | 4 | 27 | +++ | 0 | M | 35 | |
| 5 | 7 | 4 | 27 | +++ | 0 | M | 28 | |
| 6 | 30 | ½ | 22 | + | 0 | M | 44 | Unresolved pneumonia |
| 7 | During lysis | 12 | 21 | +++++ | 0 | M | 25 | |
| 8 | During lysis | 5 | 25 | +++ | 0 | M | 29 | Still has fever due to pleurisy |
| 9 | 1 (past crisis) | 4 | 25 | +++++ | 0 | M | 35 | |
| 10 | 10 (past crisis) | 12 | 24 | +++ | 0 | M | 44 | |
| 11 | 21 | 4 | 24 | ++++ | 0 | M | 53 | Lysis |
| 12 | 11 (past crisis) | 12 | 24 | +++ | 0 | M | 54 | |
| 13 | 2 (past lysis) | ½ | 24 | ++++ | 0 | M | 33 | |
| 14 | 3 (past lysis) | 12 | 20 | Weak + | 0 | M | 22 | |
| 15 | 8 (past crisis) | 2½ | 16 | + weak | 0 | M | 33 | |
| 16 | 2 (past crisis) | 8 | 16 | ++ | 0 | M | 22 | Slight hemolysis of serum |
| 17 | 14 (past crisis) | ..... | 16 | + weak | 0 | M | 20 | |
| 18 | 1½ (past crisis) | ..... | 16 | ++++ | 0 | M | 23 | |
| 19 | 7 (past crisis) | ..... | 16 | 0 | 0 | M | 19 | |

It would appear from these results that during an attack of pneumonia, the ferment content of the blood is increased. This increase is especially noted during, or just after, the crisis, and rapidly disappears in the convalescence.

This corresponds very well with our clinical knowledge of the disease, and with its short-lived immunity. It coincides also with the view I advanced in a previous paper as to the probable source of the ferment in this disease. The source is probably the consolidated lung, which in the stage of gray hepatization contains an enormous amount of pure ferment. Osler states that, as far as can be demonstrated by physical signs, the lung may be clear by the eighth day after crisis.

Recently Jobling, Eggstein, and Petersen[13] have demonstrated an increase in the antitryptic power of the blood serum in cases of pneumonia, tuberculosis, and pregnancy. This work is supported by that of Plaut,[14] who obtained positive Abderhalden tests with various inorganic absorbing substances, as kaolin, talc, barium sulphid, and infusorial earth.

*Malaria.*—Fourteen cases of malaria were studied, thirteen of which were of the tertian type and one of the estivo-autumnal type. They were taken at various stages of the disease. Most of the cases were studied after the cessation of the chills, following the administration of quinin. Every case gave a positive reaction, but great variation in intensity of reaction was noted. At the beginning of the work it was thought that shortly after a chill, with the rupture of many red blood cells, a demonstrable increase in the ferment content of the blood might be detected. This surmise was not borne out by the results as shown in Table 2. From a study of these figures, it would appear that shortly

TABLE 2

MALARIA

| Number | Duration of Disease | Time Since Last Meal in Hours | Time of Incubation in Hours | Ninhydrin Reaction | Control Reaction | Sex | Age | Remarks |
|---|---|---|---|---|---|---|---|---|
| 1 | ..... | 5 | 24 | ++++ | 0 | M | 52 | Tertian |
| 2 | 2 months..... | 5 | 23 | ++++ | 0 | M | 58 | Autumnal |
| 3 | 10 days..... | 4 | 23 | + | 0 | M | 57 | Tertian |
| 4 | Last chill 3 days before | 5 | 23 | + | 0 | M | 43 | Tertian |
| 5 | Last chill 2 days before | 5 | 23 | + | 0 | M | 17 | Tertian |
| 6 | 3 weeks. Last chill 5 days before | 4 | 23 | + | 0 | M | 51 | Tertian |
| 7 | 1 month. Last chill 7 days before | 4 | 25 | ++++ | 0 | M | 41 | Tertian |
| 8 | 4 weeks..... | 5 | .. | +++ | 0 | M | 44 | Tertian |
| 9 | 3 weeks. Last chill 4 days before | 5 | 23 | +++ | 0 | M | 34 | Tertian |
| 10 | 11 days. Last chill 3 days before | 5 | 23 | + | 0 | M | .. | Tertian |
| 11 | 9 days. Last chill 1 hour before | 4 | 25 | ++ | 0 | M | 35 | Tertian |
| 12 | 15 days. Last chill 24 hours before | 4 | 25 | ++++ | 0 | M | 36 | Tertian, no quinin |
| 13 | 18 days. Last chill 10 days before | 4 | 23 | ++++ | 0 | M | 26 | Quinin |
| 14 | 1 week. Last chill 18 hours before | 4 | 23 | +++ | 0 | M | 17 | Hemolyzed serum |
| 15 | 8 hours..... | 5 | 28 | + | 0 | M | 20 | |

13. Jour. Exper. Med., 1915, 21, p. 239.
14. München. med. Wchnschr., 1914, 61, p. 238.

after a chill there is a rather large amount of ferment in the blood. After quinin administration, and control of the chills, a period follows in which the blood is relatively poor in ferment. When convalescence is fully established, and the patient apparently well, the ferment content of the blood increases markedly. Quinin appears to have no inhibitory effect on the action of the ferments themselves, since cases taking large amounts often gave strong reactions.

*Acute Articular Rheumatism.*—The cases examined were in various stages of the disease, and the diagnosis was based on careful physical examination, together with a complete history of the case. No doubtful cases of possible gonorrheal or septic arthritis were used.

TABLE 3

ACUTE ARTICULAR RHEUMATISM

| Number | Duration of Disease | Time Since Last Meal in Hours | Time of Incubation in Hours | Ninhydrin Reaction | Control Reaction | Sex | Age | Remarks |
|---|---|---|---|---|---|---|---|---|
| 1 | 2 weeks..... | 5 | 22 | ++ | 0 | M | 55 | Light attack; no fever |
| 2 | 4 weeks..... | 5 | 22 | +++ | 0 | M | 21 | No fever |
| 3 | 2 weeks..... | 4 | 22 | + faint | 0 | M | 38 | Temp. 101 |
| 4 | 4 weeks..... | 5 | 22 | + | 0 | M | 28 | Temperature 100 three days previously |
| 5 | 3 weeks..... | 5 | 22 | + faint | 0 | M | 35 | Temp. 101 |
| 6 | ..... | 4 | 18 | +++ | 0 | M | 14 | Mitral regurgitation |
| 7 | 6 weeks..... | 5 | 22 | 0 | 0 | M | 27 | Two glasses milk 2½ hours and ½ hr. prev. |
| 8 | ..... | 5 | 18 | ++ | 0 | M | 25 | No fever for several days |

The results are shown in Table 3. From a study of this, it would seem that in general the reaction is relatively weak during the early stage of the disease while the patient is feverish, and gradually increases in intensity during the period of convalescence when the case is progressing favorably. However, enough cases have not been examined to determine the prognostic value of this phenomenon. It is probable that the reaction gets weaker, or entirely disappears, after complete recovery from the infection, as is suggested by Case 7. This would also coincide with our clinical knowledge regarding the short period of immunity following an attack of acute articular rheumatism.

Until more extensive studies are made, it is impossible to state whether this mobilization of ferment is to be regarded as an etiologic factor, or merely as a concomitant factor in the development of an immunity to this disease.

*Typhoid Fever.*—Ten cases of typhoid fever were studied. These were all carefully selected cases, each giving either positive agglutination tests, or a positive blood culture. The results obtained (Table 4) are somewhat difficult to interpret. The reaction was positive in every case, but the variation in intensity seemed to follow no definite variation in the clinical course of the disease. The series is too short to permit any definite conclusions, but it appears probable from the results that in the second week of the disease the ferments are increased to a considerable extent, and that this increase gradually

TABLE 4

TYPHOID FEVER

| Number | Duration of Disease | Time Since Last Meal in Hours | Time of Incubation in Hours | Ninhydrin Reaction | Control Reaction | Sex | Age | Remarks |
|---|---|---|---|---|---|---|---|---|
| 1 | 9 days..... | 5 | 23 | + | 0 | M | 18 | |
| 2 | 8 weeks..... | 4 | 22 | ++++ | 0 | M | 19 | Recrudescence second week |
| 3 | 10 days..... | 7 | 22 | +++ | 0 | M | 13 | Very toxic |
| 4 | 6½ weeks..... | 5 | 23 | ++ | 0 | M | 27 | |
| 5 | 6 weeks..... | 4 | 22 | +++ | Sl. color | M | 21 | Control serum heated only to 50 C. |
| 6 | 2 weeks..... | 5 | 23 | Trace | 0 | M | 24 | |
| 7 | 5 weeks..... | 5 | 22 | + | Sl. color | M | 38 | |
| 8 | 1 week..... | 4 | 27 | ++++ | 0 | M | 25 | |
| 9 | 5 weeks..... | 8 | 24 | ++++ | 0 | M | 36 | Very toxic |
| 10 | 6 weeks..... | 4 | 24 | + | 0 | M | 30 | |

disappears in the later weeks of the disease, except possibly in the very toxic cases.

*Meningitis.*—Meningitis was next investigated, and it was found that in this condition the blood was relatively poor in ferment. This is as might be expected, as the inflammatory reaction is taking place chiefly outside the blood stream, and hence the foreign proteins in the form of bacteria and their toxic products are not present in the blood in great numbers. Hence we might expect to find few ferments mobilized against them in the blood serum. This can be seen by a study of Table 5.

TABLE 5

MENINGITIS

| Number | Duration of Disease | Time Since Last Meal in Hours | Time of Incubation in Hours | Ninhydrin Reaction | Control Reaction | Sex | Age | Remarks |
|---|---|---|---|---|---|---|---|---|
| 1 | ? | Several | 22 | Negative | 0 | M | 37 | Semicomatose |
| 2 | ? | 3½ | 22 | Faint trace | 0 | M | 50 | Pneumococcal or epidemic |
| 3 | ? | Several | 24 | Negative | 0 | M | 25 | Epidemic |
| 4 | 18 days | 4 | 21 | Faint trace | 0 | M | 20 | Tuberculous |
| 5 | ..... | 3½ | 22 | Negative | 0 | M | 30 | Wassermann + |

Of the five cases studied two were tuberculous, one of which gave a faint positive reaction. This slight reaction might have been due to a focus of tuberculosis elsewhere in the body, as I have found that tuberculosis of the lungs gives a faint positive reaction in the majority of cases. One of epidemic meningitis gave a faint positive reaction, but this case had a concomitant chronic nephritis. One epidemic, and one syphilitic, meningitis gave absolutely negative results.

*Pulmonary Tuberculosis.*—Of six cases studied, a very weak reaction was obtained in four, and a negative reaction in two cases, as shown in Table 6. The negative reactions occurred in cases of a very chronic type, not very toxic, and without fever. In all, however, tubercle bacilli had been found in the sputum before the cases were used in this series. It is probable that the

positive reaction in the more rapidly advancing cases may be explained, in part at least, on the basis of a mixed infection. Whether this reaction will prove to be of value as a means of prognosis in a given case cannot be determined by this short series of cases; further work is necessary to determine this point.

TABLE 6

TUBERCULOSIS

| Number | Duration of Disease | Time Since Last Meal in Hours | Time of Incubation in Hours | Ninhydrin Reaction | Control Reaction | Sex | Age | Remarks |
|---|---|---|---|---|---|---|---|---|
| 1 | 6 weeks..... | 4 | 19½ | Trace | 0 | M | 29 | Acute pneumonic phthisis |
| 2 | 6 months..... | 4 | 19½ | Trace | 0 | M | 40 | No fever |
| 3 | 1 year..... | 4½ | 19½ | Negative | 0 | M | 46 | No fever |
| 4 | 1 year..... | 5 | 24 | Negative | 0 | M | 25 | Very chronic; no fever |
| 5 | 6 months..... | 5 | 24 | Trace | 0 | M | 46 | Rapid course. Temp. 101 |
| 6 | 2 months..... | 5 | 24 | Trace | 0 | M | .. | Acute progressive. Temperature 101 |

*Tabes Dorsalis and General Paresis.*—These diseases were studied because they represent a different type of infection from the other groups. The cases were in various stages, and some were treated while others were not. The cases were all in adult men with the exception of one case of congenital tabes in a boy of fifteen. All specimens of blood were taken in the same way, and the periods of dialyzation were as nearly equal as possible, with the exception of the first three cases of tabes.

TABLE 7

TABES DORSALIS

| Number | Duration of Disease | Time Since Last Meal in Hours | Time of Incubation in Hours | Ninhydrin Reaction | Control Reaction | Sex | Age | Remarks |
|---|---|---|---|---|---|---|---|---|
| 1 | 2 years..... | 5 | 20 | ++++ | 0 | M | 26 | Stood at room temperature 28 hours |
| 2 | 2 months..... | 5 | 20 | ++++ | 0 | M | 34 | Stood at room temperature 28 hours |
| 3 | 4 months..... | 5 | 20 | +++++ | 0 | M | 35 | Stood at room temperature 28 hours |
| 4 | 1 year..... | 4 | 24 | + | 0 | M | 52 | |
| 5 | ..... | 4 | 24 | ++ | 0 | M | 55 | |
| 6 | 3 years..... | 4 | 24 | 0 | 0 | M | 46 | Slight hemolysis |
| 7 | 3-4 years..... | 6 | 23 | Very faint | 0 | M | 40 | Gastric crisis |
| 8 | 4 months..... | 4 | 23 | ++ | 0 | M | 25 | |
| 9 | 1 year..... | 4 | 23 | + | 0 | M | 38 | |

The results are shown in Tables 7 and 8. The reaction is positive in fourteen of fifteen cases. The reactions were relatively stronger in the cases of general paresis than in the cases of tabes. The first three cases of tabes are not comparable with the other cases, because the serum was dialyzed twenty hours in the incubator and then placed twenty-four hours at room temperature,

before the dialyzation was interrupted. Therefore, the reactions were stronger than those of the other cases of tabes, as might be expected, and approached those of the general paresis cases. This corresponds with our clinical knowledge concerning these diseases. General paresis is a rapidly advancing disease, and the destructive processes are going on rapidly. The duration of the disease is relatively short. In tabes we are dealing with an essentially slow process, and destructive processes are advancing very slowly. In the active process, we should expect the mobilization of a rather large amount of ferment, while in the relatively quiescent process, we should expect relatively little of the ferment to be mobilized in excess of the normal. This is apparently what happens in these conditions. The effect of treatment could not be judged in this short series.

TABLE 8

PARESIS

| Number | Time Since Last Meal in Hours | Time of Incubation in Hours | Ninhydrin Reaction | Control Reaction | Sex | Age | Remarks |
|---|---|---|---|---|---|---|---|
| 1 | 3½ | 22 | + | 0 | M | 33 | Doing well under salvarsan |
| 2 | 3 | 22 | ++++ | 0 | M | 35 | |
| 3 | 3 | 22 | +++ | 0 | M | 42 | |
| 4 | 5 | 24 | +++ | 0 | M | 44 | Cerebrospinal syphilis |
| 5 | 3 | 22 | ++++ | 0 | M | 15 | Congenital tabes. Optic atrophy |
| 6 | 4 | 22 | ++++ | + | M | 34 | Taboparesis |

TABLE 9

CASES OF PREGNANCY

| Number | Period of Gestation in Months | Time Since Last Meal in Hours | Time of Incubation in Hours | Ninhydrin Reaction | Control Reaction | Remarks |
|---|---|---|---|---|---|---|
| 1 | ? 5 | 5 | 22 | +++ | I.S+P<br>0 | Clinical examination confirms diagnosis |
| 2 | 9¼ | 4 | 16 | +++ | S<br>0 | |
| 3 | 9¾ | 5 | 16 | +++ | I.S+P<br>0 | |
| 4 | 10 | 4 | 16 | +++ | S<br>0 | |
| 5 | 9¼ | 4 | 16 | +++ | S<br>0 | |
| 6 | 9¾ | 5 | 16 | ++ | S<br>0 | |
| 7 | 8¾ | 4 | 16 | ++ | S<br>0 | Placenta previa |
| 8 | 9 | 4 | 16 | ++ | S<br>0 | |
| 9 | 5 | 5 | 22 | +++++ | I.S+P<br>0 | Threatened abortion |
| 10 | 4 | 5 | 21 | ++++ | I.S+P<br>0 | Threatened abortion |

I have incorporated in this paper a series of cases of pregnancy and of the puerperal state so that a means of comparison might be at hand to judge the strength of the ferment activity in these conditions, as compared with that in the various diseases considered in this paper. These results are shown in Tables 9 and 10, respectively. These tests were made under the same conditions as the tests in the infectious diseases. The same tissue was used as a

substrate, in the same amounts, and, as nearly as possible, the period of dialysis was the same. The reactions were fully as strong, or even stronger, in some of the cases of infectious disease as in the strongest case of pregnancy. However, it will be noticed that there is a more uniform intensity in the cases of pregnancy. This may be explained on the assumption that in healthy women at about the same period of gestation, about the same amount of ferment is mobilized. It is possible also, as I have previously pointed out, that the source of ferment may be different in pregnancy from that in the other conditions. It seems probable that the source of the ferment in pregnancy may be at least two-fold. The ferment may be, as Abderhalden teaches, mobilized by the body to break down and destroy the protein of the placental villi that break off, and are found in the blood stream. Or it may be, as I have said before, that the

TABLE 10
PUERPERAL CASES

| Number | Length of Time After Parturition | Time Since Last Meal in Hours | Time of Incubation in Hours | Ninhydrin Reaction | Control Reaction | Remarks |
|---|---|---|---|---|---|---|
| 1 | Just after delivery | 10 | 22 | ++++ | S<br>0 | |
| 2 | 8 hours..... | 5 | 22 | + | I.S.+P.<br>0 | Wassermann + |
| 3 | 1½ days..... | 5 | 22 | +++ | I.S.+P.<br>0 | |
| 4 | 3 days..... | 5 | 22 | ++ | I.S.+P.<br>0 | |
| 5 | 3 days..... | 3 (liquid) | 22 | ++ | S<br>0 | Postpartum eclampsia |
| 6 | 7 days..... | 4 | 22 | ++ | S<br>0 | Acute puerperal mania |
| 7 | 5 days..... | 5 | 22 | ++ | I.S.+P.<br>0 | |
| 8 | 6½ days..... | 5 | 22 | +++ | I.S.+P.<br>0 | |
| 9 | 8 days..... | 5 | 22 | +++ | I.S.+P.<br>0 | |
| 10 | 13 weeks..... | 4½ | 24 | ++ | I.S.+P.<br>0 | Nursing baby |

placenta, which is a loose structure very rich in ferment and engaged in the later months of pregnancy in an immense amount of metabolic activity, both anabolic and catabolic, cannot contain all of the ferments within itself. Hence a leakage occurs of ferment into the maternal blood. These considerations may explain, in part at least, the regularity with which the increase in ferments can be demonstrated in pregnancy, and also the relative constancy of the reaction as to intensity in normal women at the same period of gestation. Experiments are now in progress whereby it is hoped that some more definite light may be thrown on this point.

From a study of these results as a whole, it seems clear that we must regard the proteolytic ferments of the blood as being raised above the normal in nearly all cases of infectious diseases. It seems probable also that this mobilization of ferments takes place in response to certain definite conditions that arise in the blood stream during the course of an infection. As has been shown by many authors, there

is a mobilization of ferments in the blood of all animals after the parenteral injection of a foreign protein. This phenomenon seems to be in the nature of a protective reaction of the body against the possible harmful effects that might arise from the toxic radicle which forms part of every protein molecule. According to Vaughan[15] and many other authors, in cases of infectious disease we must assume that we have a condition in which the body is constantly being invaded by particles of foreign protein, and that this protein in the shape of bacteria, and their metabolic products, is in the blood stream, as well as in the tissues. It is logical to assume that, as a means of defense against this invasion, the body mobilizes ferments that have the power to break down the protein to the end products of tryptic digestion, which are powerless to cause harm in the body.

If, then, these ferments are mobilized in these conditions, they should be capable of demonstration by the Abderhalden dialysis method, and also by the antitrypsin determination method. This has already been done by Jobling, Eggstein, and Petersen[16] and by several others for some of the diseases that I have considered in this paper.

It appears to me that the demonstration of the ferments of the blood by the antitrypsin method and by the Abderhalden dialysis method depend on one and the same thing: an increase in the tryptic power of the blood serum above the normal.

It has long been known that if the trypsin content of the blood be artificially increased by the injection of solutions of trypsin, the antitrypsin in the blood also is increased in direct proportion. Wells[17] cites Hildebrand as having first described this phenomenon, and as pointing out that it depended upon the same principle as the production of immunity in animals by the injection of various proteins. Von Dungern[18] immunized animals against bacteria, and obtained an immune serum against their proteolytic ferments.

Therefore it appears that this work fits in with, and corroborates other work. It is merely a new way of demonstrating what has long been thought probable on theoretical grounds. It confirms, by complementing, the work done by the antitrypsin method in these conditions by other authors.

15. Protein Split Products in Relation to Immunity and Disease, Philadelphia and New York, 1913.
16. Jour. Exper. Med., 1915, 21, p. 239.
17. Chemical Pathology, 1907.
18. München. med. Wchnschr., 1898, 45, p. 1040.

One rather interesting point in these results is the fact that the ferment activity of the serum apparently bears no relation to the leukocytic content of the blood from which the serum was derived. Thus it will be seen by examining the tables, that in the cases of malaria, tuberculosis, and typhoid, diseases in which we find a leukopenia, the reaction is often strong; while in meningitis, and in some of the cases of pneumonia, in which leukocytosis is early, and constantly high, the reaction may be weak, or even absent. This speaks against the view that the ferment is derived from the leukocytes, altho it may be that in the diseases which are characterized by a leukopenia, we have to deal with an overdestruction, rather than an underproduction, of the leukocytes. If this were true the apparent discrepancy between the leukocytic and ferment content of the blood might be explained.

I wish to point out in this connection that I do not consider the dialysis method a delicate one. In working with so many variable factors, qualitative reactions must be accepted with a certain degree of reserve, and only accepted as facts when sufficient evidence is acquired by this and other methods to give weight to conclusions drawn from the results obtained.

## CONCLUSIONS

In the infectious diseases the ferment content of the blood is increased above the normal in most cases.

This increase is capable of demonstration by the Abderhalden dialysis method.

The variation in intensity of the reaction in the various diseases at different stages of the infection, may prove of value in diagnosis or prognosis; but there are so many variable factors in the carrying out of the test, as described by Abderhalden, that too much must not be expected from the test along these lines.

The increase in antitryptic power of the blood occurs in these diseases, in all probability, in response to the increase in the tryptic content of the serum, which in turn is probably due to the presence of a foreign protein in the blood stream.

Acute infections in which the reaction between the infecting organism and the body defenses takes place outside the blood stream, cause relatively little increase in the ferment content of the blood serum, as measured by this method.

Pregnancy and the puerperal state, together with many other conditions, give reactions that cannot be differentiated from these reactions. This destroys its practical value as a diagnostic measure.

The source of the ferment is probably not to be found in the leukocytes, because the reaction was often strongly positive in cases in which there was a low leukocyte count—malaria, pregnancy, typhoid, general paresis—and frequently weak in conditions in which the leukocyte count was high—meningitis and pneumonia before the crisis.